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Liver enzymes, race, gender and diabetes risk: the Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Aims—To examine the associations of the liver enzymes alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transferase with diabetes risk and to determine whether associations differ by race and/or gender. We hypothesized that all liver enzymes would be associated with diabetes risk and that associations would differ by race and gender.

Methods—Prospective cohort of 7495 white and 1842 black participants without diabetes in the Atherosclerosis Risk in Communities Study. Poisson and Cox models adjusted for demographic, socio-behavioural, and metabolic and health-related factors were used.

Results—During a median of 12 years of follow-up, 2182 incident cases of diabetes occurred. Higher liver enzyme levels were independently associated with diabetes risk: adjusted hazard ratios (95% confidence intervals) were 1.68 (1.49–1.89), 1.16 (1.02–1.31) and 1.95 (1.70–2.24) comparing the highest with the lowest quartiles of alanine aminotransferase, aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT), respectively. gamma-Glutamyl transferase was most strongly related to diabetes risk, even at levels considered within normal range (< 60 U/l) in clinical practice. Adjusted incidence rates by quartiles of liver enzymes were similar by gender but higher in black versus white participants. Nonetheless, relative associations of alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase (GGT) with diabetes were similar by race (*P* for interactions > 0.05).

Conclusions—Compared with aspartate aminotransferase and alanine aminotransferase, gamma-glutamyl transferase was more strongly associated with diabetes risk. Our findings suggest that abnormalities in liver enzymes precede the diagnosis of diabetes by many years and that individuals with elevated liver enzymes, even within the normal range as defined in clinical practice, are at high risk for diabetes.

Introduction

Non-alcoholic fatty liver disease (NAFLD) includes a spectrum of disorders ranging from hepatic steatosis to cirrhosis and is often diagnosed in the presence of cryptogenic elevated

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Competing interests

Nothing to declare.

liver enzymes [1]. Previous studies have reported that NAFLD and elevated liver enzymes are associated with an increased risk of diabetes [2]. There are substantial underlying differences in the distributions of liver enzymes by gender [3,4] and race [1,3]; however, it is unclear if these differences translate to differences in risk of diabetes. Some previous studies have suggested no gender differences in risk of diabetes [5] while others have shown a slightly different risk in women than in men [6], but men are more likely to have elevated liver enzymes [7]. Black people are at increased risk for diabetes, but are less likely to have elevated aminotransferases than white people [3]. Few studies investigating the association of liver enzymes with diabetes risk have included large numbers of black participants [8,9] and none have explored potential effect modification by race.

The objective of this study was to examine the comparative associations of the liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT) with incident diabetes in the large, community-based Atherosclerosis Risk in Communities (ARIC) Study. We also sought to determine whether any associations of liver enzyme levels with diabetes risk differed by gender and race. We hypothesized that all liver enzymes would be associated with diabetes risk and that associations would be stronger in white people compared with black people and stronger in men than in women because of differences in the underlying distribution of liver enzymes by race and gender.

Patients and methods

Study population

The ARIC Study is an ongoing community-based prospective cohort of 15 792 middle-aged adults from four communities in the USA: Washington County, Maryland; Forsyth County, North Carolina; suburbs of Minneapolis, Minnesota; and Jackson, Mississippi. Approximately 90% of the black participants were recruited from Jackson, Mississippi, with the remaining recruited from Forsyth County, North Carolina. The first visit took place from 1987 to 1989 and participants have been followed since then [10]. Liver enzymes were measured from stored blood samples originally collected at visit 4 (1996–1998), which was attended by 11 656 participants (80% of living participants) and is the baseline for the present analysis. Starting after visit 4, diabetes status has been assessed via self-report during annual telephone calls performed by trained research assistants to all participants. Data from annual telephone calls (> 90% participation rates) and vital status were available up to December 31, 2008.

Of the 11 656 participants who attended visit 4, we excluded participants with prevalent self-reported diabetes ($n = 1365$), participants with high alcohol consumption (men > 21 drinks/week, women > 14 drinks/week) ($n = 253$) [11], participants who self-identified as other than white or black race ($n = 56$), who were missing data on liver enzymes ($n = 150$) and who were missing data on other covariates of interest ($n = 495$), leaving 9337 participants (including 1062 participants with undiagnosed diabetes defined as fasting glucose ≥ 7 mmol/l or by a 2-h glucose ≥ 11.1 mmol/l during an oral glucose tolerance test) for the present study. Institutional review boards at each clinical site approved the study and written informed consent was obtained from all participants.

Liver enzymes

The enzymes ALT, AST, and GGT were measured in 2010–2011 from visit 4 plasma samples (stored at 80°C since collection in 1996–1998) using an Olympus AU400e automated chemistry analyser according to the manufacturer's protocol. Intra-assay coefficients of variation were 11.1% for ALT, 8.5% for AST and 9.3% for GGT.

Definition of incident diabetes

We classified persons as having incident diabetes if they reported a physician diagnosis of diabetes or current diabetes medication use during an annual telephone call. Specifically, the questions ‘Has a doctor ever said you have diabetes (sugar in the blood)?’ and ‘Did you take any medications during the past 2 weeks for diabetes or high blood sugar?’ were asked. The date of the annual telephone call where the participant first reported diabetes was used as a proxy for the date of diagnosis. The end of follow-up was the earliest date of self-reported diabetes, death, study dropout or the latest date of the annual telephone call where no diabetes was reported. This definition of self-reported diabetes in ARIC has been previously reported to have sensitivity ranging from 56% to 80% and specificity ranging from 85% to 91%, depending on the reference definition used [12].

Covariates

All variables of interest were measured at visit 4, with the exception of education, which was assessed at visit 1 (1987–1989). Variables included in our models were: age, gender, race (black, white), education (< high school; high school or equivalent; > high school), family income (< \$35 000/year; \$35 000/year; missing), cigarette smoking (never, former, current), alcohol consumption (never, former, current low [women < 7 drinks/week; men < 14 drinks/week], current moderate [women 8–14 drinks/week; men 15–21 drinks/week]), BMI, waist circumference, triglycerides, HDL-cholesterol, systolic blood pressure, diastolic blood pressure, use of hypertension medication, high sensitivity c-reactive protein and serum glucose.

Statistical analysis

Using the distributions in the overall analytical population, we categorized each liver enzyme into quartiles. We used adjusted Poisson regression to obtain incidence rates [95% confidence intervals (CIs)] per 1000 person-years for diabetes. Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% CIs for incident diabetes. The proportional hazards assumptions were checked with the use of Schoenfeld residuals and graphic methods. Restricted cubic spline models were implemented in the Cox models to assess the continuous relationships between liver enzymes and incident diabetes. Model 1 included the demographic variables (age, gender, and race). Model 2 included the variables in Model 1 plus socio-behavioural variables (education, family income, cigarette smoking and alcohol consumption). Model 3 included the variables in Model 2 plus metabolic and health-related variables (BMI, waist circumference, triglycerides, HDL-cholesterol, systolic blood pressure, diastolic blood pressure, use of hypertension medications, and C-reactive protein). We tested for trend across the median of the liver enzyme quartiles and formally tested for multiplicative interaction by race and gender in each model by adding product terms to the models. We also performed analyses using race- or gender-specific quartiles to assess whether any differences in risk resulted from underlying differences in enzyme distributions.

We conducted a sensitivity analysis adding glucose, physical activity and history of cardiovascular disease to our models. In order to assess the potential for reverse causality, we conducted a sensitivity analysis in which we excluded participants with prevalent diabetes at visit 4 not only defined by self-report, but also defined by a fasting glucose ≥ 7 mmol/l or by a 2-h glucose ≥ 11.1 mmol/l during an oral glucose tolerance test ($n = 8275$ after exclusions). We also performed sensitivity analyses using liver enzyme quartiles among 8578 participants with ‘normal’ liver enzyme levels (ALT ≤ 40 U/l, AST ≤ 40 U/l and GGT ≤ 60 U/l) [11] and among 1884 participants who self-identified as ‘never drinkers.’

All reported *P*-values are two-sided, and $P < 0.05$ was considered statistically significant. Analyses were performed using STATA version 12.

Results

Overall, the mean age was 63 years, 57% were female and 20% were black (Table 1). Black participants were slightly younger and were more likely to be male compared with white participants. The overall distributions of the liver enzymes differed by race and by gender (see the Supporting Information, Figure S1). Median ALT levels were higher in white participants than in black participants (13 U/l versus 12 U/l, $P < 0.001$), a 7.7% difference. Median AST levels did not differ in white or in black participants (both 18 U/l). Median GGT levels were lower in white participants than in black participants (20 U/l vs. 25 U/l, $P < 0.001$), a 25.0% difference. Men tended to have higher levels of liver enzymes than women. Specifically, median ALT levels were 20.0% higher (15 U/l versus 12 U/l, $P < 0.001$), median AST levels were 5.3% higher (19 U/l vs. 18 U/l, $P < 0.001$) and median GGT levels were 25.0% higher (24 U/l vs. 18 U/l, $P < 0.001$) in men than in women.

During a median of 12 years of follow-up, there were 2182 incident cases of diabetes. Figure 1 shows the adjusted incidence rates (95% CIs) per 1000 person-years for diabetes by quartile of ALT (a), AST (b) and GGT (c) in black and white participants. The absolute risk of diabetes tended to be higher in black participants than in white participants across quartiles of all liver enzymes and was significantly higher for ALT Q1, Q3, and Q4, AST Q1 and Q2, and GGT Q4. There was a stepwise increase in the incidence of diabetes with increasing quartile of ALT and GGT for both black participants and white participants. The absolute risk for diabetes was similar between men and women for all quartiles of all liver enzymes (all $P > 0.05$) (Figure S2).

Table 2 shows the adjusted hazard ratios (95% CIs) for incident diabetes by quartiles of ALT, AST and GGT. The hazard ratios were attenuated with progressive adjustment for confounding and metabolic variables. In Model 3, compared with Q1 of ALT, Q2, Q3 and Q4 were significantly associated with an increased risk of diabetes (P for trend < 0.001). For AST, only Q4 was significantly associated with increased risk for diabetes compared with Q1 (HR 1.16, 95% CI 1.02–1.31). We found that GGT was most strongly associated with diabetes risk of the three liver enzymes (Table 2, Figure 2). Indeed, even after adjustment for both AST and ALT, GGT remained a significant independent risk factor for diabetes (GGT Q4 versus Q1: HR 1.84, 95% CI 1.60–2.13). Additional adjustment for glucose, physical activity, and history of cardiovascular disease in the models did not appreciably alter our estimates (data not shown). In all models for ALT, AST and GGT, α -values for interaction by race and by gender were not statistically significant (all P interaction > 0.05). However, in race-stratified analyses (see the Supporting Information, Table S1), among white participants, ALT Q2, Q3 and Q4 were all significantly associated with diabetes risk, while among black participants only ALT Q4 was significantly associated with risk of diabetes. Analyses using race- (Table S2) and gender- (Table S3) specific quartiles showed similar risk of diabetes comparing white participants with black participants and men with women for all enzymes. Figure 2 shows the adjusted hazard ratios (95% CIs) from restricted cubic spline models depicting the continuous relationship between the liver enzymes and incident diabetes. We observed continuous, dose–response relationships between each liver enzyme, especially ALT and GGT, and diabetes risk.

The results for the association of ALT and GGT with diabetes risk remained significant in sensitivity analyses. In analyses excluding participants with prevalent diabetes defined by either self-report, fasting glucose, or 2-h glucose measured after an oral glucose tolerance test, ALT Q4 and GGT Q2, Q3 and Q4 remained significantly associated with risk of

diabetes, while the results for AST were not significant. In analyses restricted to participants with 'normal' liver enzyme levels (ALT < 40 U/L and AST < 40 U/L, and GGT < 60 U/L), ALT Q2, Q3 and Q4 and GGT Q2, Q3 and Q4 remained significantly associated with risk of diabetes, while AST was not significant. In analyses restricted to 'never drinkers', ALT Q2 and Q4 and GGT Q2, Q3 and Q4 remained significantly associated with increased diabetes risk, but AST was not significant.

Discussion

In this large, community-based cohort, elevated levels of ALT, AST and GGT were all associated with incident diabetes. Of the three liver enzymes, GGT was most strongly associated with diabetes risk. We found that the associations of liver enzymes with risk of diabetes were continuous (no clear threshold) and extended well within the 'normal' range of each liver enzyme. There were significant racial differences in the absolute risk of diabetes by quartiles of all liver enzymes at baseline, but the relative associations were not modified by race. There were no gender differences in the absolute or relative risk by liver enzyme quartile with diabetes.

Previous large, prospective studies demonstrating a relationship between elevated liver enzymes and risk of diabetes have largely been performed in white [2,13–18] or Asian [19–21] populations. Our findings confirm the association of liver enzymes with diabetes in both black and white populations [3,8]. It is notable that the associations of liver enzymes with diabetes risk were continuous, extended well within the 'lower-normal' range of each liver enzyme (significantly increased risk of diabetes for Q2 vs. Q1 for ALT and GGT), and remained significant when using race-specific and gender-specific quartiles. Our results suggest large differences in absolute diabetes risk across quartiles of liver enzymes where, for each liver enzyme value, the associated absolute risk for diabetes was higher for black participants than for white participants even after adjustment for known diabetes risk factors. This result is consistent with the well-established higher risk of diabetes in black individuals compared with white individuals [5]. However, the relative risks were similar in white participants and black participants and there was no evidence of a race or gender interaction in the observed associations, suggesting that elevated liver enzyme levels in these population subgroups should be interpreted similarly.

The primary biological mechanism postulated to link NAFLD with the development of diabetes involves hepatic lipid accumulation and insulin resistance. The presence of excess lipid accumulation in hepatocytes has been shown to lead to hepatic insulin resistance (impaired suppression of glucose production by insulin in hepatocytes), which contributes to systemic insulin resistance and diabetes [22]. It has also been suggested that the presence of reduced muscle insulin sensitivity is associated with increased hepatic *de novo* lipogenesis [22]. Putative explanations for the differences in the prevalence of both elevated liver enzymes and NAFLD in race/ethnic groups include differences in adiposity and insulin resistance [3,23,24]. Although obesity is associated with elevated liver enzymes and NAFLD, and black populations have higher levels of obesity, they tend to have paradoxically lower liver enzyme levels (ALT and AST) and a lower prevalence of NAFLD compared with white or Hispanic populations [23]. It has been hypothesized that black populations may have a different metabolic response to obesity and insulin resistance compared with white or Hispanic populations [24]. Using data from the Dallas Heart Study, Guerrero *et al.* [24] found that despite similar levels of insulin resistance, black populations are less likely to have accumulation of triglycerides in visceral fat compared with white or Hispanic populations. Our results suggest that although absolute prevalence of elevated liver enzymes and of diabetes differs by race, the relative contribution of hepatic insulin resistance to the onset of diabetes is similar by race.

In our study, GGT was the liver enzyme most strongly associated with diabetes risk and this association persisted in participants who had never consumed alcohol. The independent association of GGT with diabetes in our study is consistent with other studies reporting strong associations of elevated GGT with diabetes [2,13,14,19,20]. A possible explanation for the stronger association of GGT with diabetes compared with that of ALT and AST is that GGT is more associated with hepatic steatosis [25], which is strongly linked to diabetes. In addition, GGT is involved in the catabolism of glutathione and is associated with increased oxidative stress, which has been implicated in the development of insulin resistance and diabetes [25].

Certain limitations should be considered when interpreting the results of this study. Previous studies have demonstrated short-term variability in liver enzymes [26] and we had only single measurements of each of the enzymes. In addition, we did not have any direct measures of NAFLD (e.g. imaging or biopsy) and using liver enzymes as a surrogate measure may underestimate the NAFLD, which may have led to an attenuated association. Although we excluded participants with excess alcohol consumption, it is possible that individuals in this study may have had elevated liver enzymes from causes other than NAFLD (e.g. hepatitis B, hepatitis C or haemochromatosis). However, in random subsamples of ARIC participants, there were low prevalences of hepatitis C (0.8%) [27] and haemochromatosis (0.2%) [28]. We used self-reported diabetes obtained from annual telephone calls as our outcome, which may have resulted in some misclassification and we did not have information on undiagnosed cases of diabetes during follow-up. However, this outcome has been previously shown to have reasonable validity for the detection of diabetes cases in the ARIC cohort [12]. It has also been shown in the ARIC cohort that associations of traditional risk factors with diabetes tend to be underestimated when diabetes is self-reported compared with diabetes definitions that use glucose criteria [29]. We also used the date of the annual telephone call as a surrogate for the date of diabetes diagnosis. Because participants could have had diabetes for some months before the reporting date, it is possible that our study underestimates the magnitude of the effect of liver enzymes on diabetes risk. As in any epidemiological study, our results are generalizable to populations similar to the study cohort (middle-aged black and white community-dwelling adults). Our study also has a number of important strengths, including large sample size, rigorous measurement of confounders and comparison of the three different liver enzymes that are used in clinical practice. In addition, our population comprised a large number of black participants (20%), allowing us to assess possible racial differences.

In conclusion, we found that liver enzymes were independently associated with diabetes even after adjustment for known diabetes risk factors. We observed a continuous increase in risk for diabetes with higher baseline levels of liver enzymes, even within ranges that are considered 'normal.' We found that GGT was a stronger risk factor for diabetes compared with either AST or ALT, suggesting that GGT may have a greater association with the risk of diabetes. There was no evidence for effect modification by age, gender or race. The clinical practice guidelines from the American Diabetes Association identify fatty liver disease as 'common comorbid condition' that should be screened for and treated in people with diabetes [30]; however, our data suggest that abnormalities in liver enzymes can precede the diagnosis diabetes by many years and that individuals with elevated liver enzymes, even within the normal range, and particularly GGT, are at high risk of diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Adjusted incidence rates [95% confidence intervals (CI)] per 1000 person-years for incident diabetes by quartiles of liver enzymes at Atherosclerosis Risk in Communities (ARIC) visit 4 (1996–1998) stratified by race: (a) alanine aminotransferase (ALT), (b) aspartate aminotransferase (AST), (c) gamma-glutamyl transferase (GGT)). Rates were adjusted for age, gender, education, family income, smoking, alcohol consumption, body mass index, waist circumference, triglycerides, HDL-cholesterol, systolic blood pressure, diastolic blood pressure, use of hypertension medications, and C-reactive protein. † $P < 0.05$ comparing white participants vs. black participants

FIGURE 2.

Adjusted hazard ratios (HR) [95% confidence intervals (CI)] for incident diabetes from restricted cubic spline models centred at the median of each liver enzyme: (a) alanine aminotransferase (ALT), (b) aspartate aminotransferase (AST), (c) gamma-glutamyl transferase (GGT). Hazard ratios were adjusted for age, sex, race, education, family income, smoking, alcohol consumption, body mass index, waist circumference, triglycerides, HDL-cholesterol, systolic blood pressure, diastolic blood pressure, use of hypertension medications and C-reactive protein.

Table 1

Participant characteristics overall and stratified by race, the Atherosclerosis Risk in Communities (ARIC) Study, visit 4 (1996–98).

	Overall (N = 9,337)	White (n = 7495)	Black (n = 1842)
Age (years), mean (SD)	62.7 (5.6)	62.9 (5.6)	61.6 (5.6)
Female, %	57.3	44.6	34.9
Field centre			
Washington County, Maryland, %	27.3	33.9	0.0
Suburbs of Minneapolis, Minnesota, %	29.6	36.9	0.0
Forsyth County, North Carolina, %	25.4	29.2	10.2
Jackson, Mississippi, %	17.7	0.0	89.8
Education			
Less than high school education, %	17.4	13.3	34.1
High school education or equivalent, %	42.7	46.2	28.8
More than high school education, %	39.9	40.6	37.1
Family income < \$35 000/year, %	46.9	41.0	70.8
Cigarette Smoking			
Current, %	14.2	13.4	17.5
Former, %	43.1	45.1	35.2
Never, %	42.6	41.5	47.3
Alcohol Consumption			
Current moderate (8–14 drinks/week for women; 15–21 drinks/week for men), %	3.9	4.4	2.1
Current low (< 7 drinks/week for women; < 14 drinks/week for men), %	45.6	51.1	24.0
Former, %	29.7	27.4	38.8
Never, %	20.8	17.1	35.1
Liver enzymes in men			
ALT (U/l), median (IQR)	15 (11–19)	15 (11–20)	13 (10–19)
AST (U/l), median (IQR)	19 (16–23)	19 (16–22)	19 (16–24)
GGT (U/l), median (IQR)	24 (18–35)	24 (18–34)	29 (21–42)
Liver enzymes in women			
ALT (U/l), median (IQR)	12 (9–15)	12 (9–16)	11 (8–14)
AST (U/l), median (IQR)	18 (15–21)	18 (15–21)	17 (15–20)
GGT (U/l), median (IQR)	18 (13–28)	17 (13–26)	23 (16–32)

	Overall (N = 9,337)	White (n = 7495)	Black (n = 1842)
Body mass index 30 kg/m ² , %	32.5	29.4	44.7
High waist circumference (men > 102 cm; women > 88 cm), %	63.4	62.5	66.9
Triglycerides (mmol/l), mean (SD)	1.58 (0.91)	1.67 (0.94)	1.22 (0.62)
HDL cholesterol (mmol/l), mean (SD)	1.31 (0.42)	1.29 (0.42)	1.39 (0.43)
Systolic blood pressure (mmHg), mean (SD)	126.8 (18.7)	125.2 (18.1)	133.0 (19.7)
Diastolic blood pressure (mmHg), mean (SD)	71.2 (10.2)	69.9 (9.8)	76.5 (10.5)
Hypertension medication use, %	33.2	29.2	49.5
Fasting blood glucose (mmol/l), mean (SD)	5.68 (1.08)	5.63 (0.97)	5.89 (1.45)
High sensitivity C-reactive protein (nmol/l), median (IQR)	21.9 (9.5–49.5)	20.0 (9.5–45.7)	3.3 (1.3–7.3)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; SD, standard deviation; IQR, interquartile range.

Table 2

Adjusted hazard ratios (95% confidence intervals) for incident diabetes by quartiles of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT) at Atherosclerosis Risk in Communities (ARIC) visit 4 (1996–1998)

	Model 1	Model 2	Model 3
ALT Q1 (< 10 U/l)	1.00 (reference)	1.00 (reference)	1.00 (reference)
ALT Q2 (11–13 U/l)	1.17 (1.03–1.33)	1.19 (1.05–1.35)	1.17 (1.03–1.33)
ALT Q3 (14–17 U/l)	1.36 (1.20–1.54)	1.40 (1.23–1.58)	1.24 (1.09–1.41)
ALT Q4 (> 18 U/l)	1.96 (1.74–2.20)	2.00 (1.78–2.25)	1.68 (1.49–1.89)
<i>P</i> -value for trend	< 0.001	< 0.001	< 0.001
<i>P</i> -value for interaction by race	0.041	0.052	0.053
<i>P</i> -value for interaction by gender	0.521	0.685	0.457
AST Q1 (< 15 U/l)	1.00 (reference)	1.00 (reference)	1.00 (reference)
AST Q2 (16–18 U/l)	0.89 (0.79–1.00)	0.92 (0.81–1.03)	0.98 (0.87–1.10)
AST Q3 (19–22 U/l)	0.91 (0.81–1.02)	0.94 (0.83–1.06)	0.98 (0.87–1.11)
AST Q4 (> 23 U/l)	1.11 (0.98–1.25)	1.15 (1.02–1.30)	1.16 (1.02–1.31)
<i>P</i> -value for trend	0.029	0.007	0.003
<i>P</i> -value for interaction by race	0.243	0.158	0.318
<i>P</i> -value for interaction by gender	0.331	0.366	0.186
GGT Q1 (< 15 U/l)	1.00 (reference)	1.00 (reference)	1.00 (reference)
GGT Q2 (16–21 U/l)	1.68 (1.46–1.93)	1.67 (1.45–1.93)	1.33 (1.16–1.54)
GGT Q3 (22–31 U/l)	2.31 (2.01–2.65)	2.32 (2.02–2.66)	1.61 (1.40–1.85)
GGT Q4 (> 32 U/l)	2.93 (2.56–3.35)	2.97 (2.60–3.40)	1.95 (1.70–2.24)
<i>P</i> -value for trend	< 0.001	< 0.001	< 0.001
<i>P</i> -value for interaction by race	0.212	0.153	0.726
<i>P</i> -value for interaction by gender	0.794	0.802	0.856

Model 1: demographic variables (age, gender, and race). Model 2: Model 1 plus socio-behavioural variables (education, family income, cigarette smoking, and alcohol consumption). Model 3: Model 2 plus metabolic and health-related variables (BMI, waist circumference, triglycerides, HDL-cholesterol, systolic blood pressure, diastolic blood pressure, use of hypertension medications, and C-reactive protein).